ORAL ARGUMENT NOT YET SCHEDULED

No. 24-1049

In the

United States Court of Appeals

for the

District of Columbia Circuit

VANDA PHARMACEUTICALS INC.,
Petitioner,

– v. –

UNITED STATES FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs; NAMANDJÉ BUMPUS, PH.D., in her official capacity as Principal Deputy Commissioner of Food and Drugs; XAVIER BECERRA, in his official capacity as Secretary of Health and Human Services; and the DEPARTMENT OF HEALTH AND HUMAN SERVICES,
Respondents.

On Petition for Review of an Order of the
Food and Drug Administration
Agency Case No. FDA-2022-N-2390

PETITIONER'S OPENING BRIEF

PAUL W. HUGHES
SARAH P. HOGARTH
CHARLES SEIDELL
NICOLE WITTSTEIN
McDermott Will & Emery LLP
500 North Capitol Street NW
Washington, DC 20001
(202) 756-8000
phughes@mwe.com

Counsel for Petitioner

CERTIFICATE AS TO PARTIES, RULINGS, AND RELATED CASES

Parties and amici. The parties before the Court are petitioner Vanda Pharmaceuticals Inc. and respondents the U.S. Food and Drug Administration; Robert M. Califf, in his official capacity as Commissioner of Food and Drugs; Namandjé Bumpus, Ph.D., in her official capacity as Principal Deputy Commissioner of Food and Drugs; Xavier Becerra, in his official capacity as Secretary of Health and Human Services; and the U.S. Department of Health and Human Services. There are no other parties or amici at this time.

Rulings under review. The ruling under review is the Order signed on February 29, 2024, by Namandjé N. Bumpus on behalf of the Commissioner of Food and Drugs refusing approval of sNDA 205677-004, denying Vanda a hearing on approvability, and denying Vanda's request for summary judgment, Docket No. FDA-2022-N-2390-0033. This Order is attached as Exhibit A to the petition for review; it is also published at 89 Fed. Reg. 16,001 (Mar. 6, 2024).

Related cases. This case has not previously been before this Court. Counsel is aware of no related cases pending in this Court. In the U.S. District Court for the District of Columbia, Vanda filed an action seeking to compel respondents to act on Vanda's supplemental new drug application (sNDA) and request for a hearing on the application within the timelines

prescribed by 21 U.S.C. § 355, resulting in partial summary judgment for Vanda. *See Vanda Pharms., Inc. v. FDA*, No. 22-CV-2775, 2024 WL 307387 (D.D.C. Jan. 26, 2024) (Nichols, J.). Counsel is aware of no other related cases.

CORPORATE DISCLOSURE STATEMENT

Pursuant to Circuit Rule 26.1, Vanda certifies the following: Vanda, a global biopharmaceutical company focused on the development and commercialization of innovative therapies, is a publicly held corporation and has no parent companies. BlackRock, Inc., a publicly held company, owns 10% or more of Vanda's stock. No other publicly held corporation or entity owns an interest of 10% or more in Vanda.

/s/ *Paul W. Hughes*

TABLE OF CONTENTS

TABLE OF AUTHORITIES*

Cases

---

* Authorities marked with an asterisk are those on which we chiefly rely.

Cases—continued

Constitutional Provision and Statutes

Constitutional Provision and Statutes—continued

Regulations

Other Authorities

GLOSSARY OF ABBREVIATIONS

CDER	Center for Drug Evaluation and Research
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
ICSD-3	International Classification of Sleep Disorders, Third Edition
ICD-10	International Classification of Diseases, Tenth Revision
JLD	jet lag disorder
JLQ	Jet Lag Questionnaire
KSS	Karolinska Sleepiness Scale
LPS	latency to persistent sleep
NDA	new drug application
Non-24	Non-24-Hour Sleep-Wake Disorder
PGI-S	Patient Global Impression of Severity
PSQ	Post-Sleep Questionnaire
sNDA	supplemental new drug application
SMS	Smith-Magenis Syndrome
TST	total sleep time
$TST_{2/3}$	total sleep time in the first two-thirds of the night
VAS	Visual Analog Scale

INTRODUCTION

Millions of Americans travel cross-country and overseas every year. Many experience jet lag—the severe insomnia or excessive daytime sleepiness that results from the misalignment between environmental cues and the body's internal circadian clock after rapidly traveling across several time zones. Yet no therapy is currently approved by the Food and Drug Administration (FDA) to treat jet lag disorder. Hetlioz® should be the first.

Hetlioz® (tasimelteon) is a melatonin receptor agonist that entrains the body's circadian rhythm. Marketed by Vanda Pharmaceuticals Inc. (Vanda), Hetlioz® is the first FDA-approved therapy to treat two debilitating circadian-rhythm disorders—Non-24-Hour Sleep Wake Disorder (Non-24) and nighttime sleep disturbances in Smith-Magenis Syndrome (SMS). Hetlioz® has a remarkable safety profile, which FDA has repeatedly acknowledged. Indeed, Hetlioz® has been on the market for more than 10 years, and there have been no safety concerns relating to physical dependence or abuse potential—in stark contrast to certain other sleep-related therapeutics. Hetlioz® does not have any statistically significant effect on next-day driving performance, a rarity for drugs that treat sleep-related conditions.

Hetlioz® treats jet lag disorder by resetting the circadian rhythm, which is initially calibrated with the traveler's originating time zone, to align with a desired bedtime in the new time zone. Vanda conducted three

clinical studies confirming Hetlioz®'s efficacy in treating jet lag disorder. These studies include a real-world jet travel study and laboratory phase-advance studies that induce the circadian-rhythm mismatch that causes jet lag. Vanda's studies demonstrate that patients taking Hetlioz® reached persistent sleep 15 to 21.5 minutes faster, slept an hour longer in the first two-thirds of the night when jet lag's forces are at their strongest, and slept 74 to 85 minutes longer total than subjects taking placebo after experiencing the rapid time-shift that causes jet lag disorder. These significant sleep benefits are highly meaningful improvements for patients. Vanda thus applied to FDA for approval to market Hetlioz® to treat jet lag disorder.

Despite the overwhelmingly strong clinical results and Hetlioz®'s longstanding safety record, FDA rejected Vanda's application and refused to even hold the approvability hearing the statute mandates. *See* 21 U.S.C. § 355(c)(1)(B). FDA erred procedurally by denying the hearing, by refusing to even consider Vanda's voluminous expert evidence, and by failing to consider narrowed indication language. The result from this deficient process was arbitrary and capricious substance: As we document, several of FDA's essential conclusions are indefensible.

The crux of the problem is that FDA has construed the statute to erect an echo-chamber, where the only expert analysis that matters is FDA's own.

That approach is irreconcilable with both the Federal Food, Drug, and Cosmetic Act (FDCA) and the Administrative Procedure Act (APA). Drug sponsors have a right to challenge FDA's conclusions via their own expert evidence—and when they submit such evidence, as Vanda has done, FDA must address it. Had it done so fairly, FDA would have approved Vanda's application.

JURISDICTION

FDA had jurisdiction to review and render a final decision on Vanda's supplemental new drug application under 21 U.S.C. § 355(b) and (c) via delegation from the Secretary of Health and Human Services to the Commissioner of Food and Drugs (*id.* § 393(d)).

This Court has jurisdiction under 21 U.S.C. § 355(h). Vanda timely petitioned for review on March 5, 2024, within sixty days of FDA's order dated February 29, 2024. *Id.*

ISSUE STATEMENT

Whether FDA's order refusing to approve and denying Vanda a hearing on approvability of its supplemental new drug application for Hetlioz® to treat jet lag disorder must be set aside because—

(I) FDA followed an unlawful process by (A) denying Vanda a hearing on approvability contrary to 21 U.S.C. § 355(c)(1)(B) and

FDA regulations; (B) disregarding Vanda's expert evidence entirely; and (C) refusing to consider a narrower indication like it has for similarly situated applicants;

(II) FDA's analysis of Vanda's evidence was arbitrary, capricious, or contrary to law for (A) unjustifiably disregarding Vanda's primary endpoints and (B) irrationally criticizing Vanda's secondary endpoints, which are immaterial in any event; or because

(III) FDA's order was adopted in violation of the Appointments Clause.

PERTINENT STATUTES AND REGULATIONS

Relevant provisions are set out in an addendum to the brief.

STATEMENT

A. Legal background

The FDCA conditions the introduction of "any new drug" into interstate commerce on FDA approval. 21 U.S.C. § 355(a). An innovator seeking to market a new drug must submit a new drug application (NDA) to FDA with "substantial evidence" that the drug is both safe and effective for its intended use. *Id.* § 355(d). A supplemental new drug application (sNDA) qualifies a previously approved drug for a new use.

"Substantial evidence" means evidence from "adequate and well-controlled investigations" from which "qualified" "experts" could "fairly and responsibly conclude[] that the drug will have the effect it purports to have."

21 U.S.C. § 355(d)(5).

After an innovator submits its application to FDA for review, the FDCA requires FDA to take one of two actions within 180 days: FDA "shall either (A) approve [an] application if [it] finds that none of the grounds for denying approval … applies, or (B) give the applicant notice of an opportunity for a hearing … on the question of whether such application is approvable." 21 U.S.C. § 355(c)(1). In the latter case, if the applicant accepts the opportunity for a hearing, the hearing "shall commence" within 120 days of FDA's notice. *Id.* § 355(c)(1)(B).

After the hearing, FDA "shall issue an order approving the application" unless it finds that one of six statutory grounds for refusing an application is met. 21 U.S.C. § 355(d). Relevant here, the fifth of those grounds permits FDA to deny an application where "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have" in the proposed labeling. *Id.*

Notwithstanding Section 355(c)(1)(B)'s plain language requiring either approval or a hearing, FDA regulations permit denying a hearing and entering summary judgment against an applicant if "it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application." 21 C.F.R. § 314.200(g).

In reality, FDA's summary-judgment procedure has fully supplanted the statutory hearing process. Though only five notices of opportunity for a hearing on drug applications have issued since 2018, not a single applicant has received a statutory hearing. Docket Nos. FDA-2022-N-2390, FDA-2021-N-0874, FDA-2021-N-0208, FDA-2018-N-0188. FDA remains as averse to hearings as it has been since the 1970s. *See Edison Pharm. Co. v. FDA*, 513 F.2d 1063, 1072 (D.C. Cir. 1975) (noting FDA's "failure to grant a hearing to any applicant casts doubt upon [its decision's] good faith"); Joel E. Hoffman, *The FDA's New Forms of Public Hearing—Choosing Among Alternatives*, 32 Food Drug Cosmetic L.J. 330, 330, 333 (1977).

B. Factual background

1. Vanda and its drug Hetlioz®

Vanda is a pharmaceutical innovator focused on the development and commercialization of innovative therapies to address high-priority unmet medical needs and improve the lives of patients. One of its drugs is Hetlioz® (tasimelteon), a melatonin receptor agonist that entrains a person's circadian rhythm—the body's natural 24-hour sleep-wake cycle—to initiate sleep at an appropriate time.

FDA has approved Hetlioz® to treat two rare and debilitating conditions characterized by circadian-rhythm dysfunction: Non-24 and nighttime

sleep disturbances in SMS. Vanda has studied Hetlioz® to treat other circadian-rhythm-related disorders.

2. Jet lag disorder

Jet lag disorder, also referred to as jet lag or JLD, is one kind of circadian rhythm disorder. AR8606-8607. Jet lag occurs when rapid travel across time zones causes a mismatch between the day/night cycle and the body's expectation (i.e., the person's natural sleep-wake cycle). AR14237-14238. Sufferers experience disturbed sleep and/or daytime sleepiness, among other secondary symptoms. AR14238.

Millions of travelling Americans—especially pilots, flight attendants, and frequent business travelers—routinely experience impairment from the symptoms of jet lag. *See* AR14442. It causes traffic accidents, disrupts business meetings, and impedes professional athletic performances. AR14442, AR14486-14487. Jet lag disorder impairs diplomats and deployed military personnel. AR14442-14444. And beyond its immediate effects, studies suggest jet lag exposure may have significant long-term consequences, including increased risk of cancer, infertility, and heart disease. AR14445.

Despite all this, there are currently no FDA-approved therapies to treat jet lag. AR14459. Those suffering from jet lag symptoms instead resort to off-label drug cocktails that come with significant safety risks like drowsiness, impairments to motor function, and dependency (AR14460-14463);

melatonin supplements for which there is no FDA-approved use and questionable efficacy (AR14463-14465); unworkable light treatments (AR14456-14458); or simply suffering through the jet lag, with all its attendant harms.

3. Hetlioz® effectively treats jet lag disorder.

It need not be this way. FDA and Vanda agree that Hetlioz® would be safe for use in jet lag disorder. AR18050. And Vanda has conducted extensive clinical research into Hetlioz®'s efficacy in treating jet lag. With its sNDA, Vanda submitted three pivotal clinical trials (Studies 2102, 3101, and 3107) that collectively provide substantial evidence of Hetlioz®'s efficacy in treating jet lag.

When conducting pharmaceutical clinical trials, innovators prespecify a "primary endpoint" to measure. AR14240. That is, in advance of conducting the experiment, the researcher discloses the key measurement to evaluate. AR14240. "Secondary endpoints" are additional observations recorded in the experiment that may add confirmatory evidence. AR14240.

In **Study 2102**, Vanda studied the effects of Hetlioz® by flying participants across time zones to induce jet lag. AR14265-14266. Vanda first conducted a baseline study (study 0101) in which it flew participants from the U.S. to Europe to cause either a 5-hour or 8-hour phase advance and studied their brain activity. AR14262-14265. Based on these results, Vanda determined that the first two-thirds of the night were most likely to be disturbed

by jet lag, and the worst sleep disturbance occurred on the third night. AR14264; AR14266-14267. Vanda thus selected a primary endpoint that would compare the effects of Hetlioz® versus the effects of placebo on the total sleep time (TST) during the first two-thirds of the night ($TST_{2/3}$) on the third night of travel. AR14245-14246, AR14266-14268.

Vanda then flew the 25 people who met the criteria from the U.S. to Europe again. AR14265. Each participant, randomly assigned, took either Hetlioz® or a placebo 30 minutes before their usual bedtime but in the destination's time zone. AR14266. Hetlioz® demonstrated a statistically significant improvement on its primary endpoint—$TST_{2/3}$ on night 3—over placebo. AR14266-14267.

In **Study 3101**, Vanda studied the effects of Hetlioz® by simulating jet lag in a laboratory.[2] Participants were randomly assigned to take either Hetlioz® or a placebo and then to go to bed 5 hours before their usual bedtime. AR14260. This simulates what happens to the body following eastward travel across 5 time zones (e.g., New York to London): the body must

[2] Vanda conducted two studies in laboratories, which accords with FDA regulations. *See* 21 C.F.R. § 314.126(b)(3) (directing that study subjects need only have "susceptibility and exposure to the condition against which prophylaxis is directed"). Doing so was important because "travel fatigue" and "jet lag disorder" both stem from jet travel—but only the latter is attributable to a phase shift. AR14238; AR14921. Laboratories allow study of phase shift without confounding variables, such as "alcoholic beverages." AR14921-14922.

sleep five hours earlier than it normally would to maintain the same bedtime. *See* AR14262-14263.

Vanda measured as its primary endpoint participants' "latency to persistent sleep" (or LPS)—i.e., how long it took participants to achieve 10 minutes of sleep—a measure on which Hetlioz® demonstrated a statistically significant improvement over placebo with patients falling asleep an average 21.5 minutes faster. AR14260-14261.

Study 3107 similarly studied the effects of Hetlioz® by simulating jet lag, this time for eastward travel across 8 time zones (e.g., Los Angeles to London). AR14249-14250. Vanda measured as its primary endpoint $TST_{2/3}$, and Hetlioz® showed a statistically significant improvement over placebo with patients on average sleeping roughly an hour longer in the first two-thirds of the night. AR14253-14254.

Tying all the data together, Vanda showed that patients who experience the phase advance that causes jet lag fall asleep faster and sleep longer when taking Hetlioz®. Patients fell asleep on average 15 to 21.5 minutes faster, outperforming Ambien®'s 5 to 12 minutes. AR14255-14256; AR14260-14261; AR16759.

Patients slept an average *hour* longer during the first two-thirds of the night—when jet lag's forces are strongest. AR14254; AR14628-14629. And they slept 74 to 85 minutes longer overall (depending on the study)

(AR14255-14257)—more than tripling the American Academy of Sleep Medicine's 20-minute-improvement standard (AR14684) that FDA has accepted as meaningful (AR15296-15297).

Not only did patients actually sleep longer, they reported that they felt that they slept longer. AR14261-14262.

These striking results and FDA's agreement as to Hetlioz®'s safety positioned Hetlioz® to be the first FDA-approved therapy to treat jet lag.

C. Procedural background

Vanda submitted its sNDA to market Hetlioz® for treatment of jet lag disorder on October 16, 2018. AR2. Despite the decade-long collaboration between Vanda and FDA, the agency issued a terse complete response letter saying that it would not approve the sNDA. AR2-6.

Over the next year, Vanda attempted to assuage FDA's concerns through post-action meetings, correspondence, and formal appeals. AR162-165 (summarizing efforts); *e.g.*, AR6518-6565, AR6591-6631, AR6651-6768, AR6795-6808.[3] After those efforts proved fruitless, Vanda formally requested an opportunity for its statutorily mandated hearing.

Issuing the notice triggered FDA's statutory obligation to commence Vanda's hearing within 120 days. *See* 21 U.S.C. § 355(c)(1)(B). But FDA did

[3] Vanda also brought a FOIA action—and prevailed in a contested motion for summary judgment—to obligate FDA to provide its underlying analysis of Vanda's sNDA. *Vanda Pharms. v. FDA*, 2023 WL 2645714 (D.D.C. 2023).

not. Instead, FDA forced Vanda into a protracted summary-judgment procedure with FDA's Center for Drug Evaluation and Research (CDER) as adversary to test whether Vanda could even have a hearing. Through that proceeding, Vanda submitted:

- Two declarations from Dr. Thomas Roth, Ph.D, the Emeritus Chief and Division Head of the Sleep Disorders and Research Center at the Henry Ford Health System, spanning 135 pages (AR14234-14317; AR14619-14669);
- Two declarations from Dr. Daniel Combs, M.D., a board-certified sleep medicine physician and sleep-medicine researcher, spanning 83 pages (AR14440-14492; AR14674-14703);
- A 13-page declaration from Dr. Robert Platt, Ph.D, the Albert Boehringer Chair of the Department of Pediatrics and Epidemiology, Biostatistics and Occupational Health at McGill University (AR14707-14719);
- More than 340 exhibits supporting its positions and experts' opinions;
- A 77-page opening submission (AR148-225); and
- A 76-page response to CDER's proposed order (AR14537-14613).

CDER submitted a 76-page proposed order with only a single reference, a 75-page amended proposed order (to which Vanda had no opportunity to respond), and a 33-page reply with no supporting evidence.

Following briefing, FDA failed to render a decision. A district court, in response to FDA's candid admission that it "ha[d] violated the statute" by failing to timely commence a hearing, ordered FDA to act by March 5, 2024. *Vanda Pharms. v. FDA*, 2024 WL 307387, at *3, 6 (D.D.C. Jan. 26, 2024).

In response, FDA issued its final order, signed by Principal Deputy Commissioner Namandjé Bumpus. AR17984-18079. FDA granted summary judgment to itself, denied Vanda a hearing, and refused to approve the sNDA. Though it issued a 96-page order, FDA's conclusion was that there was not even a "material issue of fact as to whether the application is approvable." AR17987.

This petition followed.

SUMMARY OF ARGUMENT

After more than a decade of conducting clinical studies to fill an unmet need, Vanda presented to FDA a robust record demonstrating Hetlioz®'s efficacy in treating jet lag disorder. FDA, however, refused to approve Vanda's application and even denied Vanda the right to a hearing enshrined in the statute. FDA's order is contrary to law and arbitrary and capricious several times over.

I. FDA employed an unlawful process.

A. The FDCA obligates FDA to provide Vanda a hearing on its supplemental new drug application. To the extent that precedent or regulations provide FDA limited discretion to deny a hearing—indeed, the statute is best read as foreclosing any such discretion—FDA had no valid basis for denying Vanda a hearing. Rather, factual disputes abound.

FDA avoided a hearing by claiming that "scientific policy and regulatory judgment" are reserved solely for resolution by FDA personnel, outside the hearing process. As FDA sees it, a dispute of fact in this context extends only to disputes over the literal numeric values obtained in clinical studies. Per FDA, whether those studies were properly designed and whether an expert would find substantial evidence of the drug's efficacy are *not* factual issues at all.

FDA's position would upend the hearing process Congress designed: What FDA characterizes as "scientific policy and regulatory judgment" are the *essential* questions underlying drug approval for which Congress provided a hearing right. FDA's contrary position seeks to establish an echo chamber—as FDA would have it, only the views of its experts matter, and drug innovators are foreclosed from presenting their own evidence.

B. FDA compounded this error by refusing to even consider the substantial expert testimony Vanda presented. FDA cannot disregard hundreds of pages of sworn expert declarations, backed by hundreds of exhibits (many of which are peer-reviewed journal articles) simply by labeling them "conclusory." FDA's manifest failure to consider voluminous evidence disputing its conclusions was unlawful.

C. FDA further erred by failing to consider a narrower indication. FDA does not dispute that Vanda's application provides, at minimum, substantial evidence that Hetlioz® is efficacious in treating insomnia or sleep disturbance associated with jet lag disorder. FDA's procedural objection—that it evaluates an NDA slavishly based on the precise indication initially identified—conflicts with years of agency practice. As FDA admits, it routinely approves drugs with indications narrower than that stated in the application. FDA cannot explain why it has treated Vanda so differently.

II. FDA's order is arbitrary and capricious on the substance. Vanda's clinical studies demonstrate overwhelmingly positive evidence confirming Hetlioz®'s efficacy. FDA's efforts to pick-apart Vanda's blatantly successful clinical studies all fail. Vanda selected appropriate primary end-points—scores of evidence proves the point. And while Vanda need not demonstrate secondary endpoint success, its studies did so anyway.

Below, we detail these issues. Reversal of FDA's denial would be appropriate—FDA has essentially no evidence or reasoning to rebut Vanda's comprehensive record. At minimum, these disputes confirm beyond all doubt that Vanda is entitled to a hearing where FDA will be obligated, for the first time, to actually address Vanda's extensive evidence.

III. Finally, FDA's order violates the Appointments Clause. Dr. Bumpus does not qualify as a principal officer, and thus she lacked the requisite authority to deny Vanda's sNDA. Separately, no statute authorized Dr. Bumpus's appointment.

STANDING

Because Vanda is the "object of [FDA's] action," "there should be 'little question'" that Vanda satisfies the elements of standing. *Sierra Club v. EPA*, 292 F.3d 895, 900 (D.C. Cir. 2002); *see* AR18078.

STANDARD OF REVIEW

Section 355(h) permits an "appeal" to this Court of an FDA order refusing approval of a new drug application.

When FDA denies an applicant a hearing and enters summary judgment in FDA's favor, the Court "determine[s] whether … the deficiencies [FDA] finds conclusively render the study inadequate or uncontrolled in light of the pertinent regulations." *Cooper Lab'ys, Inc. v. Comm'r, Fed. Food & Drug Admin.*, 501 F.2d 772, 777 (D.C. Cir. 1974) (quoting *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 622 (1973)).[4] *See also infra*

[4] 21 U.S.C. § 355(h) provides that the "findings … as to the facts" are reviewed under the "substantial evidence" standard. As the Supreme Court observed in *Weinberger*, this fact-finding standard is inapposite when assessing whether FDA can properly deny a hearing. 412 U.S. at 622 n.19.

at 22-23.[5]

Additionally, this Court must "hold unlawful and set aside agency action, findings, and conclusions" that are "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law," "contrary to constitutional right, power, privilege, or immunity," "in excess of statutory jurisdiction, authority, or limitations." 5 U.S.C. § 706; *see also Pharm. Mfg. Res. Serv. v. FDA*, 957 F.3d 254, 259 (D.C. Cir. 2020) (*PMRS*).

ARGUMENT

I. FDA EMPLOYED AN UNLAWFUL PROCESS IN REFUSING TO APPROVE VANDA'S SNDA.

A. FDA's refusal to provide a statutorily mandated hearing was unlawful.

The FDCA and implementing regulations obligate FDA to provide Vanda a hearing. FDA's contrary holding is indefensible; it seeks to construct a new category of "policy" that is neither fact (and thus outside the scope of a hearing) nor law (and thus not reviewable de novo)—but that is instead left solely to FDA to adjudicate. That is flatly wrong. While FDA may adopt "policies" to guide its adjudication, that label does not remove

---

[5] Although *PMRS* suggested that this review may be deferential (957 F.3d at 266), such an observation is in substantial tension with *Weinberger*. 412 U.S. at 622.

Moreover, forthcoming decisions in *Loper Bright Enterprises v. Raimondo*, No. 22-451 (S. Ct.) and *Relentless, Inc. v. Department of Commerce.*, No. 22-1219 (S. Ct.) may substantially restrict agency deference.

central questions underlying drug approval—such as whether a sponsor has sufficient evidence of efficacy—from the typical review framework governing issues of fact, issues of law, and mixed questions of law and fact.

1. The FDCA requires a hearing on approvability.

a. The statutory text is straightforward. After receiving an NDA or sNDA, Congress directs that FDA, within 180 days, "shall either (A) approve the application … or (B) give the applicant notice of an opportunity for a hearing." 21 U.S.C. § 355(c)(1). And, "[i]f the applicant elects to accept the opportunity for hearing, … such hearing shall commence" within 120 days of the notice. *Id.* § 355(c)(1)(B).

This statutory command is unambiguous: The word "'shall' is 'mandatory'" and "connotes a requirement." *Kingdomware Techs., Inc. v. United States*, 579 U.S. 162, 171-172 (2016). The word's mandatory nature is even clearer "[w]hen a statute distinguishes between 'may' and 'shall'" (*id.* at 172)—as Section 355 frequently does. *Compare* § 355(c)(1)(B), *with* § 355(e) ("The Secretary *may* also … withdraw the approval of an application."). Section 355(c)(1)(B) leaves no uncertainty—because FDA "shall commence" a hearing upon an applicant's request, that hearing *must* commence. And "a basic principle of administrative law is that agencies must comply with the requirements … contained in the text of applicable statutes." *City of Anaheim v. FERC*, 558 F.3d 521, 522 (D.C. Cir. 2009).

b. In a neighboring statutory context, the Supreme Court has approved limited use of a summary-judgment mechanism. In *Weinberger*, the Supreme Court addressed 21 U.S.C. § 355(e), which governs *withdrawing* a previously approved NDA (not Section 355(c)(1), relevant here, which governs *approving* an NDA). 412 U.S. 609 (1973). The Court held that FDA may deny a hearing "when it appears *conclusively* from the applicant's 'pleadings' that the application cannot succeed." *Id*. at 621 (emphasis added).

This holding is narrow. It "applies … only to those regulations that are *precise*." 412 U.S. at 621 n.17 (emphasis added). FDA may grant summary judgment only if it is apparent from "[a] mere reading" of an application that it is "totally deficient" on a well-defined, nondiscretionary regulatory requirement. By contrast, summary judgment is generally *not* appropriate if FDA's denial would draw on regulations that "are not precise" because "they call for the exercise of discretion or subjective judgment." *Id.*

Under this framework, *Weinberger* affirmed the court of appeals' holding that FDA unlawfully denied a hearing where a party "argue[d] that its submission to FDA satisfied its threshold burden" and "a majority are of the view that the submission was sufficient to warrant a hearing." 412 U.S. at 622-623.

In *John D. Copanos & Sons, Inc. v. FDA*, this Court added that, in addition to failing to comply with a "precise" regulation, summary judgment

may be appropriate "on the basis of *manifest noncompliance* with general statutory or regulatory provisions, or even on the basis of obvious noncompliance with an undisputed particularization of general statutory mandates." 854 F.2d 510, 522 (D.C. Cir. 1988).

In *Copanos*, the Court noted that the "regulations on which the FDA based its … order … [were] 'imprecise' in various places" and that "the agency's 'particularization' of these general standards has been explicitly challenged … in a number of instances where [petitioner's] non-compliance with the regulation's requirements cannot fairly be described as 'manifest.'" 854 F.2d at 522.

Weinberger and *Copanos* thus limit summary judgment to those circumstances where a drug application is so obviously (or uncontestably) noncompliant with statutory or regulatory standards that denial does not require the exercise of discretion. As the Court has explained, "when a statute or regulation utilizes but does not particularize broad judgmental concepts, and requires 'adequate and well-controlled investigations' … it is difficult to demonstrate that a submission is conclusively deficient." *Am. Cyanamid Co. v. FDA*, 606 F.2d 1307, 1312 (D.C. Cir. 1979).

c. It is not clear that *Weinberger* should be extended to Section 355(c)(1). *Weinberger* and *Copanos* addressed Section 355(e), which provides

that FDA "shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application" under certain circumstances. Section 355(c)(1) goes further, directing that a hearing "shall commence" if the applicant requests one.

"When Congress uses different language in the very same section of a statute, courts should assume that it intended that difference to have some meaning." *Ctr. for Bio. Diversity v. Regan*, 597 F. Supp. 3d 173, 205 (D.D.C. 2022). Here, the difference is clear. In 1962, as now, "commence" means to start or begin. *See Commence*, Webster's Third New International Dictionary (1961) ("[T]o initiate formally by performing the first act of"); *Commence*, Black's Law Dictionary (Rev. 4th ed. 1968) ("To perform the first act of"). The addition of the "shall commence" language to Section 355(c)(1) demonstrates Congress's intent that hearings on drug applications must *actually occur*. While FDA might fairly be said to offer an "opportunity" for a hearing despite its summary-judgment procedures, it is implausible that when FDA grants summary judgment a hearing has "commenced." Indeed, FDA's regulations state that the Commissioner "den[ies] a hearing" when he determines summary judgment is appropriate and will "grant a hearing if there exists a genuine and substantial issue of fact." 21 C.F.R. § 314.200(g)(1)-(6). Thus, while the language of Section 355(e) may be compatible with the denial of a hearing, Section 355(c)(1) is different.

d. But even assuming *Weinberger* and its progeny apply, summary judgment was improper.

Here, FDA's summary judgment did not turn on any precise regulation that Vanda allegedly failed to satisfy. None appeared in the notice of an opportunity for a hearing; it invoked only Section 355(d)(5)'s general and subjective requirement of "substantial evidence" of efficacy. AR114. When Vanda pointed this out, CDER confirmed that it was relying only on "section 505(d)(5) of the FD&C Act as the basis for not approving the sNDA." AR17786 n.80. FDA's final order was no different: FDA did not cite a single statutory or regulatory provision other than the "substantial evidence" standard and procedural summary-judgment regulations. AR17999; *see also* AR18002-18046.

Instead, FDA points only to extremely general standards, compliance with which cannot possibly be ascertained merely from the face of Vanda's submission. FDA relies on words like "appropriate," "sufficient," and "reliable," which—like "'adequate' and 'suitable'"—are "qualitative standards" that "do not lend themselves to clear-cut definition." *Weinberger*, 412 U.S. at 621 n.17. And Vanda contested each of CDER's arguments in more than 150 pages of analysis of its clinical studies and the 14,000-page record.

e. Additionally, as confirmed by extensive argument below, there are "several 'issues of fact' that are genuinely in dispute,'" precluding summary

judgment. *Copanos*, 854 F.2d at 522.

Vanda provided expert declarations from *three* experts (Dr. Roth, Dr. Combs, and Dr. Platt) addressing each of FDA's objections and explaining why they would not lead to a negative conclusion. AR14226-14436 (Roth); AR14437-14493 (Combs), AR14614-14670 (2d Roth); AR14671-14703 (2d Combs); AR14704-14821 (Platt). FDA cannot deny that each of Vanda's studies met its primary endpoint with statistical significance—its objections are thus limited to quibbles with study design. These sorts of factual disputes—such as whether patients find an extra hour of sleep meaningful (*e.g.*, *infra* at 24) and whether a patient would understand an ordinal scale of 1 to 9 (*e.g.*, *infra* at 49-50)—are plainly "genuine and substantial issue[s] of fact." *See Copanos*, 854 F.2d at 522 n.4. The entirety of Section II of this brief presents the sort of disputes that should have gone to a hearing.

2. FDA cannot arrogate to itself all questions of "scientific policy and regulatory judgment."

No fair evaluation of the record presented in this matter could yield the conclusion that "there is no genuine and substantial issue of fact which precludes the refusal to approve the application." 21 C.F.R. § 314.200(g)(1).

FDA resists this straightforward conclusion with an extraordinary—and extraordinarily misguided—tactic. In claiming that "the material facts of Vanda's application are not in dispute" (AR17988), FDA contorts what qualifies as an "issue of fact" beyond recognition. As FDA sees it, "how

CDER has exercised its scientific policy and regulatory judgment [is] not [a] factual issue[] for resolution at a hearing" (AR18064)—and is thus impervious to challenge by a drug developer.[6]

As just one example, FDA acknowledges that "CDER and Vanda agree on the numeric results of the studies included in Vanda's sNDA," including Vanda's showing of "approximately 60 minutes" of longer sleep "on the first night of advance" in Study 3107. AR18063. But whether this evidence "demonstrate[s] that tasimelteon is *effective for the treatment of jet lag disorder*," FDA claims, "is a matter of expert scientific judgment (as informed by regulatory requirements, policies, and experience) and legal analysis …, and not a factual dispute." AR18063.

Another disputed issue is whether the Karolinska Sleepiness Scale (KSS) and the Visual Analog Scale (VAS) are appropriate instruments to measure Hetlioz®'s efficacy. FDA incredibly claims that there is no "genuine and substantial issue of fact" because "CDER and Vanda agree on the *numeric results*" of these measurements. AR18033 (emphasis added). But FDA waves away the very substantial question—whether these "tools" are "appropriate to measure effectiveness for jet lag disorder"—as a non-factual question outside the permissible scope of a hearing. AR18033.

---

[6] To the extent that a regulation purportedly allows this (*see* 21 C.F.R. § 12.24(b)(1)), it is contrary to the statute, and applying it to Vanda is unlawful.

FDA is thus attempting to create a new category of adjudication—"scientific policy and regulatory judgment"—that is neither fact nor law. Because it is not fact, FDA claims it is exempt from a hearing. And because it is not law, FDA will surely disclaim de novo review.

This would upend the obvious statutory design. When Congress provided applicants a right to a hearing, it surely did not intend to limit hearings to factual disputes regarding the literal "numeric results" of clinical studies. To the contrary, "expert scientific judgment" lies at the *core* of the hearing process: Applicants may bring their own experts to bear to dispute CDER's views, and the point of the hearing is to resolve these expert disagreements.

The Court reached this precise conclusion in *American Cyanamid*, where the petitioner "presented FDA with scientific studies which in the opinion of some experts proved that Proban may be safely used" under listed conditions. 606 F.2d at 1323. Its experts "disputed FDA's interpretation and critique of the studies' results and methods" and raised "a number of material questions about the appropriateness of the methodological standards the Director attempted to graft onto the statute." *Id.* There, as here, "the papers on file in this matter generate several material issues of fact and science that FDA attempted to resolve without a hearing, in contravention" of the FDCA. *Id.*

So too in *Copanos*. Where a party's asserted "non-compliance" with the relevant "requirements cannot be fairly described as manifest," there are "'issues of fact' that are genuinely in dispute." 854 F.2d at 522. There, FDA criticized the petitioner "for the failure to install a 'primary barrier' over the mixing tanks." *Id.* at 522 n.4. "The regulation upon which the agency relied, however," did not expressly require a primary barrier—it provided only that there be "adequate control" and "when appropriate." *Id.* (quoting 21 C.F.R. § 211.46(b)). The petitioner contended that, despite FDA's judgment, a primary barrier would be purely cosmetic at best or affirmatively harmful at worst. *Id.* This Court concluded that the petitioner's "challenge (supported by expert testimony) to the agency's attempt to 'particularize'" the regulation "makes summary judgment on the … question inappropriate." *Id.* That is, disputes about "expert scientific judgment" are *definitively* the appropriate subject of a hearing.[7]

Further, FDA's regulations, promulgated after *Weinberger*, expressly reject the narrow view FDA now advances. In discussing the "issue of fact"

---

[7] *See also Warner-Lambert Co. v. Heckler*, 787 F.2d 147, 154 (3d Cir. 1986) (FDA must "give full consideration to all of the evidence that has been submitted, including expert opinions"); AR10951 (FDA guidance noting the "law is clear" that FDA must "give[] full consideration to all of the evidence that has been submitted, including expert opinions").

requirement, FDA noted that, "[w]here the issue is effectiveness, the submission of some evidence which meets all the requirements of the statute and regulations and which contains results which show that the drug is effective would … ordinarily be sufficient to justify a hearing." Requirements of Notice of Opportunity for Hearing, Request for Hearing, and Grant or Denial of Hearing, 39 Fed. Reg. 9,750, 9,755 (Mar. 13, 1974).

In response to comments highlighting the limitations on summary-judgment procedures, FDA explained that it "has no intention of denying a hearing solely because of failure to comply with the judgmental elements" of its regulations. 39 Fed. Reg. at 9,757. Instead, it resolved to invoke regulatory provisions that required application of FDA's judgment to deny a hearing only when presented with "a total failure of a study to attempt to comply with one of the 'judgmental' elements." *Id.*

FDA's newfound position is thus irreconcilable with FDA's own rules. And FDA cannot claim that its regulation means something expressly disclaimed by the preamble. *See Pub. Citizen v. Carlin*, 184 F.3d 900, 911 (D.C. Cir. 1999) (The Court "regularly rel[ies] on the preamble in interpreting an agency rule."); *Wyo. Outdoor Council v. U.S. Forest Serv.*, 165 F.3d 43, 53 (D.C. Cir. 1999) ("[T]he preamble to a regulation is evidence of an agency's contemporaneous understanding of its proposed rules.").

Stepping back, the implications of FDA's argument are astonishing.

By claiming that any application of "expert scientific judgment" is *not* a factual issue suitable for a hearing, FDA would aggrandize to itself—without the adjudicatory hearing process Congress designed—the authority to make *all* such judgments, without ever having to undergo a hearing. FDA is shockingly express in this view: It informs us that "CDER applies its clinical expertise and interpretation of the best available science … to conclude whether" the test results provided by drug sponsors "provide substantial evidence of the drug's effectiveness." AR18063. But that is the central factual question underlying drug approval. *See Edison*, 513 F.3d at 1072 (ordering FDA to hold a hearing on a disputed "threshold" issue and "all relevant issues relating to the approvability of petitioner's application").

FDA cannot reimagine the definition of a "fact" to magically remove this ultimate question—the crux of a drug application—from the ambit of a Section 355(c)(1) hearing. Nor can it be that CDER *alone* can decide this question, without so much as considering views of non-CDER experts.

At bottom, "the best available science" (AR18063) cannot be an echo-chamber of FDA's own creation. Rather, a hearing—where CDER and the applicant alike may present competing expert evidence—is the precise forum Congress designed to decide critical factual questions, such as "whether the KSS and VAS tools have been demonstrated to be appropriate to measure effectiveness for jet lag disorder" (AR18033) and whether 60 minutes of

sleep improvement demonstrates tasimelteon's effectiveness (AR18063).

B. FDA erred by categorically disregarding Vanda's experts.

In denying Vanda a hearing, FDA also refused to so much as consider the substance of sworn testimony from industry-leading experts that Vanda presented. Vanda submitted very substantial expert evidence—thorough declarations from two leading, independent experts, Dr. Roth and Dr. Combs, and a third, targeted declaration from Dr. Platt. FDA disregarded it all, simply calling hundreds of pages of sworn statements, backed by hundreds of exhibits, "conclusory." That was unlawful; again, FDA may not create a process impervious to external scrutiny.

1. Well-settled APA standards establish that "an agency's refusal to consider evidence bearing on the issue before it constitutes arbitrary agency action within the meaning of § 706." *Butte Cnty., Cal. v. Hogen*, 613 F.3d 190, 194 (D.C. Cir. 2010).

The FDCA reinforces this essential requirement. It prohibits the Commissioner from refusing an application for lack of substantial evidence unless it "consider[s] … the information submitted … as part of the application and any other information before him with respect to such drug." 21 U.S.C. § 355(d)(5).

This follows from the FDCA's efficacy standard. Per statute, "substantial evidence" of efficacy means evidence collected in clinical investigations

by "experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved" from "which it could fairly and responsibly be concluded *by such experts* that the drug will have the effect it purports or is represented to have." 21 U.S.C. § 355(d) (emphasis added).

In *American Cyanamid*, the Court explicitly relied on expert evidence submitted to consider "whether genuine issues of fact necessitating a hearing are present." 606 F.2d at 1323 n.166. It was the drug developer's "experts" who appropriately "disputed FDA's interpretation and critique of the studies' results and methods." *Id*. at 1323-1324. In all, when an applicant presents expert evidence, FDA must address it. *See also supra* at 25-27.

2. But FDA expressly refused to do so here.

To start with, FDA has not—indeed, it surely cannot—dispute the qualifications of Vanda's experts. AR14319-14436 (Roth CV); AR14495-14512 (Combs CV); AR14721-14816 (Platt CV). FDA does not deny that Vanda has presented sworn testimony from leading experts in the relevant field.

Rather, FDA offers the surprising argument that it can disregard their sworn testimony—labeling it "conclusory"—because the declarations allegedly do not contain "specifically identified reliable evidence, from, for example, literature reviews; natural history studies; qualitative studies with patients, caregivers, or other stakeholders; or quantitative studies that

support the declarant's propositions." AR18003; *see also* AR18008. FDA informs us that "unsupported opinions of declarants, regardless of their expertise, are no substitute for objective evidence." AR18065.

FDA's central claim—that Vanda's sworn declarations do not present "objective evidence" (AR18065)—is factually wrong and legally mistaken.

We urge the Court to peruse the substantial expert reports at issue. Dr. Roth's first report is 84 pages (AR14234-14317); his second is 51 pages (AR14619-14669). Dr. Combs's reports are 53 and 30 pages. AR14440-14492; AR14674-14703. Dr. Platt's report is 13 pages. AR14707-14719. While length is not itself the issue, review of these reports confirms that they contain copious "objective evidence" bearing immediately on the issues presented here. To take just a few examples:

- Dr. Roth relied on FDA reviews of three other drugs using the same endpoint as Vanda did (latency to persistent sleep (LPS)) and two peer-reviewed studies in which other researchers used the same endpoint in evaluating jet lag disorder. AR14295-14296; *see also* AR14296-14297 (similar for Vanda's other primary endpoint, $TST_{2/3}$).
- Dr. Roth relied on 13 articles and two FDA reviews confirming the validity of the Karolinska Sleepiness Scale (KSS) to measure next-day sleepiness. AR14314-14316.

- Dr. Combs similarly relied on 11 different articles confirming the validity of the KSS to measuring next-day functioning and five articles connecting the KSS's scale to assessing improvement of jet lag disorder. AR14485-14486.

FDA considered none of this. If we had space, we would cite dozens of similar examples. FDA is wrong to claim these expert declarations do not present "objective evidence."

In any event, FDA's central position—that it categorically will not consider the "opinions of declarants, regardless of their expertise"—is deeply troubling. As we explained, expert opinion is hardwired into the statutory approval criteria—the core question is whether "experts qualified by scientific training and experience" "could fairly and reasonably … conclude[] … that the drug will have the effect it purports or is represented to have." *See* 21 U.S.C. § 355(d). When an applicant presents such evidence from acknowledged experts, FDA must address it. *See*, *e.g.*, *Am. Cyanamid*, 606 F.2d at 1323-1324.

Once more, FDA's contrary position would erect an echo-chamber, where the only scientific opinions that matter are those of FDA personnel. Neither the APA nor the FDCA—not to mention basic principles of due process—can tolerate such an extraordinary proposition. When an applicant

presents scientific judgments from undeniable experts that bear immediately on the questions in dispute, FDA *must* at least consider that evidence in rendering its decision. Perhaps FDA thinks that the evidence, opinions, and conclusions from Vanda's experts are all wrong—if so, FDA must prove why. It cannot close a proceeding from external expert evidence, disallowing an applicant from testing FDA's opinions against leading experts in the field. Given that FDA refuses to allow Vanda a hearing—where Vanda would have ability to present expert testimony—it is especially pernicious that FDA refuses to consider the expert declarations that Vanda submitted in support of its hearing request.

The failure to meaningfully address the weighty expert declarations alone renders FDA's action unlawful.

C. In failing to address alternative indication language, FDA treated Vanda differently from other applicants.

Another threshold issue infected FDA's analysis: it lodged a baseless procedural hurdle to refuse deciding whether simple adjustments to the proposed indication's language would obviate its efficacy objections.

1. The FDCA requires an application to include several pieces of information, including "specimens of the labeling proposed to be used for such drug." 21 U.S.C. § 355(b)(1)(a)(i), (vi). Through a regulation, FDA added the concept of an "indication"—a shorthand for the drug's use—and requires the application to include "the drug product's proposed indications for use." 21

C.F.R. § 314.50(a)(1). The indication then appears on the drug's label alongside substantial information describing the studies supporting the drug's efficacy. It is commonplace for applicants to describe the proposed indication broadly based on the disorder the drug proposes to treat, even though the drug might target a particular feature of a condition. AR219-220 (collecting seven examples for approved drugs); AR12045; AR11258; AR11706; AR12675; AR12189; AR13926.

Vanda followed that settled practice here. As early as 2009, FDA officials dissuaded Vanda from presenting a more specific indication—like Hetlioz®'s efficacy in the sleep-disruption aspect of jet lag—claiming this was not "truly a specific indication." *See* AR6481-6483; *see also* AR17834-17835; AR18060 (CDER and FDA admitting that CDER "consistently expressed concern" about a narrower indication). FDA thus urged Vanda *not* to pursue a narrower indication.

After receiving a complete response letter, Vanda realized that FDA's objections would be obviated by simply adjusting the indication language to its earlier proposal to focus on treating sleep-related aspects of jet lag. Vanda thus promptly sought to discuss tailored indication language. AR6529; AR6631. Vanda pursued formal appeals, requesting approval based on a narrower indication. AR6656-6658; AR6802-6803.

FDA initially responded with a substantive objection. FDA told Vanda

that it would not approve such an indication because it would be "artificially narrow." AR6581; AR6606; AR6643. Vanda explained at length why this substantive objection was meritless—scores of drugs have similarly narrow indications (*see* AR6656-6658; AR6802-6803; AR219-220)—and FDA thus abandoned its "artificially narrow" objection.

Now, FDA refuses to consider a narrowed indication because of a putative *procedural* objection—that, in its sNDA application, Vanda wrote a broader indication, and did not separately include a narrower formulation. AR6788; AR6821; AR18060.

To sum up: Vanda initially proposed a narrow sleep-related indication, and FDA dissuaded it from doing so. After FDA raised objections to Vanda's evidence as satisfying a broader indication (an issue we dispute below), Vanda suggested that it return to a narrower indication. FDA first raised a *substantive* objection to that proposal—but, upon argument from Vanda showing this substantive objection meritless, FDA now claims a *procedural* objection to its consideration. FDA's ever-shifting, contradictory positions are deeply unfair.

2. FDA's procedural objection, moreover, lacks merit. FDA's own documents confirm that "[d]evelopment of final labeling is an iterative process between the applicant and FDA." AR10637. Working collaboratively to reach an agreed label, FDA and sponsors routinely narrow indications,

without requiring the sponsor to resubmit and restart the lengthy drug approval process. *See* AR10637.

There are many examples (AR219-220):

- In approving Ofev®, FDA narrowed the indication from treating "systemic sclerosis-associated interstitial lung disease" to "*slowing the rate of decline in pulmonary function* in patients with systemic sclerosis associated interstitial lung disease" (AR12045 (emphasis added)).
- In approving Pyrukynd®, FDA narrowed the indication from "[t]reatment of adult patients with pyruvate kinase deficiency" to "[t]reatment of *hemolytic anemia* in adults with pyruvate kinase (PK) deficiency" (AR11258 (emphasis added)).
- In making similar edits when approving Nulibry®, FDA observed that it revised the indication to "reflect[] the findings for which we have substantial evidence of effectiveness," whereas the "originally proposed [] indication [was] broader" (AR11853, AR11706).

We identified several more similar examples in the record. AR219-220; *see*

also AR12675; AR12189; AR13926.[8] FDA does not make other drug developers guess at the outset what indication FDA will ultimately approve.

For Vanda's sNDA, however, FDA refused this same treatment. Even when Vanda called the unequal treatment to FDA's attention (AR6656-6658, AR6802-6803, AR219-220), it refused to consider a tailored indication. FDA now admits that "final labeling can be an iterative process, and it is not unusual for CDER and an applicant to exchange proposed revisions to labeling prior to approval." AR18058. Yet its final order *again* refused to give Vanda this most basic of equal treatment. It is textbook arbitrary and capricious agency action to "appl[y] different standards to similarly situated entities" without "support[ing] this disparate treatment with a reasoned explanation and substantial evidence in the record." *Burlington N. & Santa Fe Ry. Co.*, *v. Surface Transp. Bd.*, 403 F.3d 771, 777 (D.C. Cir. 2005).[9]

---

[8] This FDA practice is hardly surprising: FDA has long recognized as part of the "iterative" process of drug approval that narrowed indications—reflected in myriad examples—are "lesser included" within a broader proposed indication. *Cf. Sierra Club v. Trump*, 929 F.3d 670 (9th Cir. 2019) ("In common usage, a general denial of something requested can, and in this case does, encompass more specific or narrower forms of that request."); *Air Transport Ass'n of Am. v. FAA*, 169 F.3d 1, 3 (D.C. Cir. 1999) (interpreting 49 U.S.C. § 40117 governing when the FAA "may approve an application" to permit "approv[ing] the application in whole or in part").

[9] In *PMRS*, this Court upheld FDA's refusal to consider a modified proposed label after the applicant requested a hearing. 957 F.3d at 263-264. But the rationale there is inapposite here. Vanda has shown that the agency routinely considers indication variations (*contra PMRS*, 957 F.3d at 264),

3. A narrowed indication would resolve all of FDA's putative objections. FDA, however, maintains that Hetlioz would *also* have to treat "impairment of next-day functioning"—i.e., an entirely different symptom of jet lag disorder. AR18056-18057. In other words, FDA, without even attempting to identify a statutory, regulatory, or even guidance-based reason, took the position that the *only* substantive ground for refusing to approve Vanda's application with a narrower indication is because the indication is tailored to a single symptom of a multi-symptom disorder. *See* AR18056-18057.

We presented 12 examples of FDA approved drugs where the indication is for a single symptom of a multi-symptom order. AR220-221. Indeed, FDA accepted a similarly narrowed indication *for this very same drug*—Hetlioz® is approved to treat the nighttime sleep disturbances in Smith-Magenis Syndrome, not the SMS condition generally. AR365. FDA has never justified why it is treating Vanda's jet lag application so differently from the reams of similarly situated applications.

II. FDA'S ANALYSIS OF VANDA'S EFFICACY EVIDENCE WAS ARBITRARY AND CAPRICIOUS SEVERAL TIMES OVER.

Beyond its procedural failings, FDA's order is substantively arbitrary and capricious. FDA will no doubt insist on blind deference to its scientific

---

and Vanda has shown that the agency lacks grounds for substantive objection in Vanda's case (*contra id.*).

judgments—but we have already explained why the Court must be cautious in accepting that contention in the context of this case. FDA has refused to so much as *consider* the countervailing expert evidence Vanda submitted, and it has denied a hearing to adjudicate these essential issues. FDA cannot invoke broad requests for deference while simultaneously denying Vanda the procedure Congress designed to allow drug sponsors to participate in the formulation of FDA's judgment. Given this backdrop, it is essential to ensure that judicial review is not a "rubber stamp [of] agency actions." *Nat'l Res. Def. Council v. Daley*, 209 F.3d 747, 755 (D.C. Cir. 2000).

A. FDA's rejection of Vanda's primary endpoints was arbitrary and capricious.

FDA's central reason for refusing Vanda's sNDA rests on a dispute regarding the primary endpoints that Vanda chose for its clinical trials. As described above, a primary endpoint is the pre-specified metric that a researcher uses to evaluate the experiment.

Because FDA has never approved a treatment for jet lag, Vanda did not have at its disposal already-accepted endpoints for its research. Vanda thus adopted two endpoints based on extensive research and evidence. Now, FDA does not *reject* these endpoints as wrong; it instead denies Vanda's application because it claims there was "inadequate justification for the primary endpoints." AR17989.

Two issues intersect. The first is, in crafting its primary endpoints,

what aspects of jet lag Vanda needed to study. The second is whether Vanda supplied adequate justifications to support the primary endpoints it chose.

1. FDA treated Vanda's application differently than other similarly situated applications.

According to the ICSD-3—on which FDA relies—jet lag is defined by three criteria, A through C:

> A. There is a complaint of insomnia or excessive daytime sleepiness, accompanied by a reduction of total sleep time, associated with transmeridian jet travel across at least two time zones.
>
> B. There is associated impairment of daytime function, general malaise, or somatic symptoms (e.g., gastrointestinal disturbance) within one to two days after travel.
>
> C. The sleep disturbance is not better explained by another current sleep disorder or medical or neurological disorder, mental disorder, medication use, or substance use disorder.

AR17985-17986; AR8606.

As Dr. Roth explains, FDA generally has not required medications for sleep disorders to demonstrate improvement on Criterion B symptoms. AR14622-14624. Insomnia, for example, has nine "Criterion B" symptoms—including fatigue/malaise, daytime sleepiness, or behavioral problems—but FDA has approved at least 18 other sleep-disorder drugs (including Ambien, Belsomra, and Lunesta) based solely on Criterion A symptom improvement, without evidence of any improvement in Criterion B symptoms. AR14623.

Dr. Roth identified only one sleep-disorder drug—Quviviq® (daridorexant)—that "demonstrated treatment of Criterion B symptoms." AR14263. For that drug, only 50 mg of Quviviq® showed statistically significant improvement in Criterion B symptoms, while 25 mg did not. AR14263. Yet FDA *approved* the 25 mg form of Quviviq®, confirming it did not require improvement in Criterion B symptoms. AR14623-14624.

Given FDA's practice across 18 different drugs, Vanda designed its primary endpoints to focus on Criterion A symptoms. And Vanda's clinical studies conclusively showed that Hetlioz® improved Criterion A symptoms for jet lag (that is, insomnia or excessive daytime sleepiness, along with a decrease in total sleep time). AR14282 (Roth) (summarizing evidence from each study).

Yet FDA insisted that Vanda also had to show improvement in Criterion B. *E.g.*, AR17986-17987, AR18011-18013. Vanda objected on the basis of disparate treatment. *See* AR14578-14579. Yet FDA's final order did not identify a *single* other sleep-disorder medication for which it required proof of efficacy in treating a Criterion B symptom before approving the application.

Instead, FDA attempted to justify its novel and unequal treatment of Vanda's application by insisting that "impairment of next-day functioning is an integral component of jet lag disorder." AR18012; *see, e.g.*, AR17986-

17987, AR18015, AR18057. To the extent this assertion has support, it derives from the ICSD-3 definition, and FDA presented it as much. *See* AR17986. But "impairment of next-day function" is a *Criterion B* symptom. FDA *still* has not offered any explanation for why jet lag's Criterion B symptoms are an "integral component" of the disorder when FDA has not held any other sleep-disorder medication to that standard.

The only other argument FDA advances is that "[a] drug that improves sleep disturbances not associated with travel … does not improve jet lag disorder." AR18012. But Criterion A already addresses this; it is attached not to sleep disturbances generally, but rather to "insomnia or excessive daytime sleepiness, accompanied by a reduction of total sleep time, associated with transmeridian jet travel across at least two time zones." AR8606.

FDA unlawfully held Vanda to a standard far more stringent than it applies to other applicants for other sleep disorders—without a reasoned explanation for the departure. This issue infects FDA's entire analysis—only by treating Vanda's application disparately could FDA claim that Vanda's endpoints failed to measure treatment effect in jet lag disorder. At minimum, this disagreement warrants a hearing.

* * *

This issue directly ties to the scope of indication point described above.

See supra at 33-38. Vanda's proposal was to narrow the indication to Criterion A symptoms. As we described, FDA has taken a similar approach in many other cases. Had it done so here, this discussion regarding Criterion B would be moot.

2. FDA wrongly disregarded Vanda's copious evidence validating that its primary endpoints appropriately measure jet lag.

As to the endpoints themselves (LPS and $TST_{2/3}$), FDA neither accepted nor rejected them; it instead asserted that Vanda provided "inadequate justification." AR17989-17990. FDA reasoned that Vanda merely asked it to "assume" that these primary endpoints are appropriate to assess tasimelteon's effect on jet lag disorder. AR18014. That is wrong. Vanda has presented extensive evidence. FDA just disregarded it.

As noted, jet lag is a transient sleep disturbance disorder characterized by "insomnia … accompanied by a reduction of total sleep time." AR8606. Jet-lag-induced insomnia presents with difficulty falling asleep and maintaining sleep. *See* AR14294-14295. Thus, endpoints tracking improved sleep initiation and increased amount of sleep are clear measures for investigating whether Hetlioz® effectively treats the sleep disturbances associated with jet lag disorder—which is precisely what Dr. Roth and Dr. Combs, undisputed experts in the field, have concluded. AR14294-14297 (Roth); AR14479-14480 (Combs).

Because FDA has not previously approved a therapy for jet lag, and thus there are no previously approved endpoints, Vanda selected LPS and TST (modified to $TST_{2/3}$ based on jet lag research) because FDA previously accepted these measures to evaluate transient sleep disturbances. AR14294-14297 (Roth).

As Dr. Roth explains, latency to persistent sleep (LPS)—which is a measure of how long it takes someone to fall asleep—makes sound scientific sense for measuring improvement of jet lag. AR14294-14296. The central problem when flying eastward across time zones is that the body must fall asleep earlier than its natural circadian rhythm expects (because it is 6 p.m. in New York when the person needs to go sleep at 11 p.m. in London). AR14628-14630 (2d Roth). Measuring whether Hetlioz® improves the time it takes someone to fall asleep in such a circumstance is a clear measure of efficacy to treat jet lag. AR14294 (Roth).

Total sleep time (TST)—the total amount of sleep—is also a natural fit for whether a drug treats jet lag. To ensure the endpoint was tailored to jet lag, Vanda conducted an entire clinical study (study 0101) in which it flew individuals to Europe and found that the first two-thirds of the night were most likely to be disturbed by jet lag. AR14262-14265 (Roth). Vanda thus determined that showing an improvement in total sleep time in the first 2/3 of the night ($TST_{2/3}$) would accurately measure Hetlioz®'s effect on

jet lag.

As Dr. Roth explains, this too makes sense: In the first 2/3 of the night, the eastbound traveler is fighting against their natural circadian rhythm (when it is 5 p.m. to 10 p.m. in New York); by the time 2/3 of the night have passed (it is now 10 p.m. in New York), the person's natural circadian rhythm is pushing the person into sleep. *See* AR14245-14246, AR14628-14630 (Roth); AR89 (FDA in 2015 agreeing that "it was open to $TST_{2/3}$ on the worst night for the primary endpoint"). Furthermore, not all individuals naturally sleep eight hours (AR14263); for those people, a TST measure based on 8 hours would reflect experiencing jet lag's effect even when sleeping their usual amount. $TST_{2/3}$ controls against that. Measuring whether Hetlioz® is statistically significantly better than placebo in improving a person's total sleep time in the first 2/3 of the night is a clear measure of whether Hetlioz® improves jet lag.[10]

Rather than assess the merits of these endpoints, FDA rejected them on the ground that Vanda was asking FDA to "*assume*" their propriety "with conclusory and unsupported contentions." AR18013-18022. But FDA cannot disregard two extensive expert declarations, peer-reviewed studies, Vanda's own study 0101, and Vanda's reasoning (crafted by its own in-house experts)

[10] More, Vanda *did* measure TST—and it favored Hetlioz® too. FDA just disregarded the evidence. AR14267-14268, AR14283, AR14285.

simply by calling them "assertions," "conclusory," "unreliable," "not specifically identified" from FDA-selected sources, not "experimental data," or "unsupported"—all the while providing *no* evidence, *nothing*, supporting any of FDA's contrary assertions.

Agency action is arbitrary and capricious if it fails to adequately consider evidence in the administrative record. *E.g.*, *Public Emps. for Env't Resp. (PEER) v. Hopper*, 827 F.3d 1077, 1089-1090 (D.C. Cir. 2016). FDA must "give full consideration to all of the evidence that has been submitted, including expert opinions" to determine whether an applicant's "studies meet the regulatory criteria and show effectiveness." *Warner-Lambert*, 787 F.2d at 154; *see also* AR10951 (FDA guidance admitting that FDA must consider "expert opinions").

Here, FDA refused to consider Vanda's impressive study results based on a claim that Vanda's endpoints have not been used in precisely the same way before, but it then refuses to address Vanda's voluminous evidence as to *why* these endpoints demonstrate efficacy. This is arbitrary and capricious.

B. FDA's rejection of Vanda's secondary endpoints was immaterial and unlawful.

As we just described, FDA should have approved the application because (a) it is sufficient for a therapy to demonstrate efficacy as to Criterion

A symptoms alone and (b) Vanda's primary endpoints sufficiently demonstrate such efficacy. Again, there is no dispute as to Vanda's overwhelmingly favorable results with its primary endpoints. FDA thus has no basis for refusing approval in light of the primary-endpoint improvement. FDA's of criticism of Vanda's secondary endpoints is thus immaterial.[11]

Even if Vanda *did* have to demonstrate efficacy as to Criterion B symptoms, Vanda's secondary endpoints *did so*. FDA's contrary positions only reveal its arbitrary and capricious reasoning. Once more, at minimum, a hearing is warranted.

1. The Karolinska Sleepiness Scale results show efficacy.

Vanda used the Karolinska Sleepiness Scale (KSS) to measure patient-reported next-day sleepiness in Studies 3107 and 2102, which, per Dr.

---

[11] Earlier in this proceeding, FDA premised its refusal to approve on the notion that subjective (or patient-reported) endpoints are "important to FDA's analysis of whether objective endpoints are clinically meaningful." AR113. But CDER (as adversary) declined to defend this standard, and FDA then expressly abandoned this contention in its final order—stating that "arguments about 'clinical meaningfulness' are immaterial to FDA's" determination. AR18051. FDA was right to abandon any reliance on a "clinical-meaningfulness" standard—it does not appear in the FDCA, and the agency has long acknowledged that it is an ad hoc creation of the agency's interpretation of precedent. AR13963 (claiming that the requirement was invented by a federal court); *accord* AR14002. Now that FDA has abandoned this argument, the secondary endpoints are irrelevant to the Criterion A factors, which are sufficient to demonstrate efficacy.

Roth, "provides the most widely recognized measure of 'sleepiness at a particular time during the day.'" AR14243 (Dr. Roth, quoting journal article); AR14314-14316. A patient's KSS score "is based on a 9-point scale" from "extremely alert" to "very sleepy, great effort to stay awake, fighting sleep." AR312. Patients treated with Hetlioz® had a significantly lower measurement of next-day sleepiness relative to placebo-treated patients. AR4188-4192, AR4212. Yet FDA refused to consider the results, summarily concluding that "Vanda has not demonstrated, on the basis of specifically identified reliable evidence, that" KSS is "appropriate for measuring" "next-day symptoms." AR18022.

First, FDA again disregards Vanda's expert evidence. Dr. Roth provided extensive analysis—and cited several articles—validating KSS as appropriate. AR14243; AR14314-14316. FDA disregards his testimony entirely.

Second, FDA again treated Vanda differently than similarly situated applicants. FDA has twice before accepted KSS to show drugs' effectiveness in treating excessive sleepiness—for armodafinil and modafinil. AR14316. FDA cannot disagree. Instead, it retorts that, because "there is no precedent for use of the KSS" to show efficacy *in jet lag* (AR18027), Vanda cannot use it here.

This reasoning is arbitrary and capricious—FDA fails to explain why

it credited KSS when approving armodafinil and modafinil but changed course with Vanda. Nor is there any reason to conclude that, just because an endpoint has not previously appeared on a label, it is invalid, as FDA acknowledges. AR18027-18028 n.155 (agreeing this is not "dispositive"). Indeed, a conclusion otherwise would all but preclude scientific advancement.

Third, FDA's substantive criticisms of the KSS scale—that Vanda somehow failed to show that patients would understand how to complete an ordinal scale from 1 to 9—are unreasoned and irrational. *See* AR18023-18024. This is the Karolinska Sleepiness Scale patients completed:

KSS – KAROLINSKA SLEEPINESS SCALE	Not Done ☐
Time of administration (*24-hr format)*	| | |:| | |
Date of administration (*DDMMMYYYY*)	
Please choose the number that best describe your sleepiness:	1 = Extremely alert 2 = Very alert 3 = Alert 4 = Rather alert 5 = Neither alert nor sleep 6 = Some signs of sleepiness 7 = Sleepy, no effort to stay awake 8 = Sleepy, some effort to stay awake 9 = Very sleepy, great effort to stay awake, fighting sleep

AR14687; AR18138.

Yet FDA says that there is no "evidence" that patients would understand how to "distinguish" between these levels of alertness to sleepiness. But, as depicted, the KSS's instructions clearly place each level of "sleepiness" option on an ordinal scale, which can be easily comprehended. AR14687.

Vanda provided evidence that patients *do* understand these differences—from two experts experienced in working with patients and studying sleep disorders. AR14663-14664; AR14686-14689. As Dr. Combs explains, "subjects, including patients in a clinical setting, would … be able to distinguish between ratings such as 'extremely alert,' 'very alert,' and 'alert,' especially when they are numbered based on severity as in the KSS scale." AR14687. And based on "[h]aving been involved in numerous sleep research trials in general, and clinical trials involving sleep drugs specifically," Dr. Roth explains that the KSS is "clear and hence interpretable" by patients completing it. AR14664. FDA simply refuses to consider Vanda's expert evidence and common sense—that patients know how scales work. That refusal "is not reasonably explained." *Mirror Lake Village, LLC v. Wolf*, 971 F.3d 373, 376 (D.C. Cir. 2020).

Fourth, FDA contends that Vanda failed to provide evidence to show that the "numeric differences in KSS scores in subjects treated with tasimelteon compared with placebo … are relevant" to Hetlioz®'s efficacy in

treating jet lag. AR18026. But FDA *admits* in the same breath that Vanda provided precisely such evidence with Vanda's experts thoroughly explaining the connection through reliance on other clinical studies—including two that, even by FDA's standards—"did examine concepts related to jet lag." AR18028. To be sure, FDA raises several trivial criticisms of these sources—rejecting them for being too "small," for having used slightly different scale wording, or not being "representative." AR18028-18030. By this logic, Vanda would have had to undertake a complete clinical trial just of its scale—to say nothing of the several clinical studies it did in jet lag. No statute or regulation requires that. The "methods of assessment of subjects' response" need only be "well-defined and reliable." 21 C.F.R. § 314.126(b)(6). Vanda presented expert evidence and several studies showing they are.

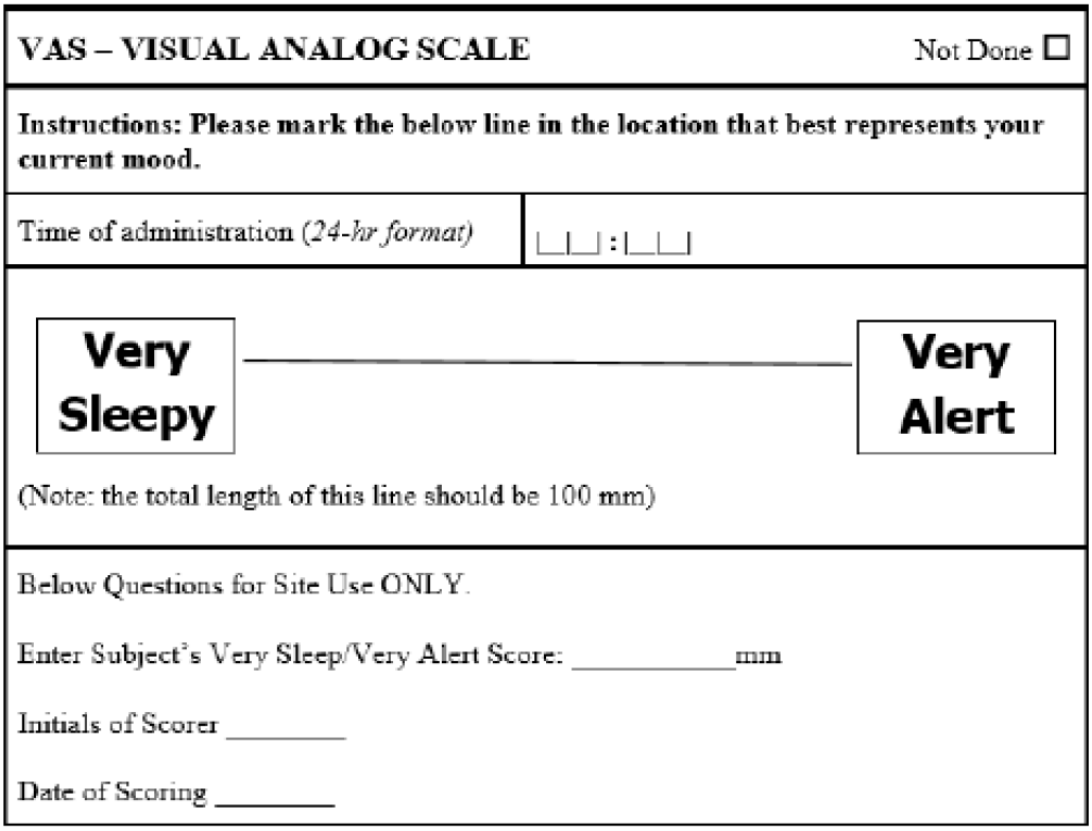
2. The Visual Analog Scale results show efficacy.

Vanda similarly pointed to its secondary endpoint measured on the Visual Analog Scale (VAS)—which asks patients to rate how they feel by selecting a point on a line from "very sleepy" to "very alert"—as providing evidence that Hetlioz® treats the Criterion B next-day impairment. Again, FDA's criticisms of VAS are contrary to the record evidence and irrational.

First, FDA's suggestion (AR18031-18032) that Vanda's VAS scale could be rejected as "unconventional" because it ran from "very sleepy" and "very alert" instead of "not sleepy" and "very sleepy" is demonstrably wrong.

As Vanda told CDER, a previous study, Hilditch (2022), "used nine VAS of mood," one of which was "alert" to "sleepy," to measure "the role of biological sex on sleep inertia symptoms." AR14592-14593. FDA does not acknowledge this point. FDA's reason for dismissing VAS as an appropriate measure of jet lag disorder—which draws on its characterization of the VAS as "unconventional" (AR18031)—is contrary to the evidence before it.

Second, FDA's criticisms related to the VAS asking subjects to indicate their "mood" on a spectrum from "very sleepy" to "very alert" distort Vanda's evidence. FDA asserts that "subjects may be confused when asked to mark their 'current mood' on a line but then find that the line does not display any descriptors of mood." AR18031-18032. This criticism disregards the context for the VAS's use of "mood," which clearly directs subjects to the singular scale ranging from "very sleepy" to "very alert":



VAS – VISUAL ANALOG SCALE Not Done ☐

Instructions: Please mark the below line in the location that best represents your current mood.

Time of administration *(24-hr format)* |_|_| : |_|_|

Very Sleepy ——————————— **Very Alert**

(Note: the total length of this line should be 100 mm)

Below Questions for Site Use ONLY.

Enter Subject's Very Sleep/Very Alert Score: _____mm

Initials of Scorer _____

Date of Scoring _____

AR14690; AR18139. Vanda's experts specifically addressed and debunked this claim with meaningful analysis—and FDA did not respond. *See* AR14655-14656 (2d Roth); AR14690-14691 (2d Combs).

FDA further criticizes Vanda for "not explain[ing] what is meant by 'mood'" or "provid[ing] any evidence that 'mood' is a relevant concept to measure in the context of jet lag disorder." AR18032. This critique makes no sense. In context, as pictured, the VAS expressly connects "mood" to the spectrum from "very sleepy" to "very alert." AR14690. And Vanda never suggested that "mood" in the abstract—as the order uses the term—is "relevant." As Dr. Roth explains, "[h]ad the VAS been measuring mood generally,

the spectrum would use corresponding language, such as 'good mood' versus 'bad mood.'" AR14655-14656 (citing AR15739, AR15743, AR15899). Instead, from the VAS's measurement of "very sleepy" to "very alert" on a line, a "patient[] would understand that the VAS is seeking the level of alertness/sleepiness rather than other aspects of mood." AR14656 (2d Roth); AR14690-14691 (2d Combs) (discussing a study that used nine VAS marks of mood from "alert" to "sleepy").

By distorting Vanda's arguments and evidence, FDA fails to rationally explain its wholesale discounting of VAS results.

3. The PSQ, JLQ, and PGI-S results show efficacy.

Vanda also provided three additional measures that assessed jet lag symptoms and patients' impression of the improvement of those symptoms:

- The Post-Sleep Questionnaire (PSQ)—which asks patients how many times they awoke in the night (wake after sleep onset or WASO), the time it took to fall asleep (latency to persistent sleep or LPS), and their total sleep time (subjective total sleep time or $TST_{subj.}$) (AR14248; AR4142-4143; AR14713);

- the Jet Lag Questionnaire (JLQ)—which asked patients who were flown abroad to assess their trouble concentrating or thinking clearly, fatigue, grogginess or sleepiness, daytime alertness and trouble with memory, hunger, and appetite (AR14249; AR1620); and

- the Patient Global Impression of Severity Scale (PGI-S)—which asked patients who were flown abroad to rate the severity of their jet lag from 1 to 4 at multiple points during the day (AR14248; AR1620).

These assessments all produced results directionally favoring Hetlioz® over placebo in treating jet lag—and some measures to a statistically significant degree. AR14258 (Roth summarizing PSQ results from study 3107); AR14261-14262 (Roth summarizing PSQ results from study 3101); AR14268 (Roth summarizing PSQ and PGI-S from study 2102).

As to these measures, FDA does not address the PGI-S at all. And FDA rejects PSQ and JLQ in a single sentence that asserts only that "Vanda did not present literature, psychometric evidence, or other information to support use of its" PSQ or JLQ. AR18022. But FDA has *no* basis—none whatsoever—for refusing to consider Vanda's expert evidence confirming the validity of these patient surveys. AR14657-14662 (Roth explaining the utility of these tools). There is certainly no statutory or regulatory requirement for "literature" or "psychometric evidence" rather than expert evidence, and FDA has no contrary evidence of its own. If FDA disagreed with Vanda's experts' conclusions, it should have come forward with its own evidence or held a hearing to explore those disagreements. But it cannot lawfully reject Vanda's evidence without any rational basis.

4. FDA's Type 1 error objection is unfounded.

Even though an overwhelming number of Vanda's secondary endpoints demonstrated Hetlioz®'s efficacy in treating jet lag, according to FDA, it can disregard this evidence entirely because Vanda did not "prespecif[y]"

a Type I error control analysis for secondary endpoints. AR18035-18036. But Vanda had no obligation to prespecify a Type I error control for these endpoints (as the order admits), and Vanda provided substantial expert testimony explaining why there is virtually no possibility that all of Vanda's favorable findings resulted from Type I error. FDA cannot disregard the law or Vanda's evidence.

In statistics, a Type I error is a false positive. AR14297. That is, a Type I error occurs when a researcher concludes that there is a statistically significant difference between a treatment group and a placebo-control group due to the treatment when instead it was just random chance. AR14297. Generally speaking, the risk of a Type I error increases as the number of things measured increases—that is, the more things you measure, the greater the likelihood some measure will be positive due to chance—a problem called "multiplicity." To counter the risk of a false-positive, researchers typically select beforehand (or prespecify) a primary endpoint and a testing order. AR14297-14298. Indeed, FDA guidance directs selecting a single primary variable for just that purpose. *See* FDA, *Guidance for Industry: E9 Statistical Principles for Clinical Trials* 6 (Sept. 1998), perma.cc/23J3-NKBL ("There should generally be only one primary variable.").

As already explained, Vanda selected primary endpoints in each of its studies—all of which achieved statistical significance using a standard confidence interval—and which provide the effective control against Type I error. AR14298 (Roth); AR14645 (2d Roth); FDA, *E9 Guidance*, *supra*, at 7, 9 ("To avoid multiplicity concerns … , it is critical to specify in the protocol the precise definition of the primary variable … ."). Vanda thus prespecified how it would control for Type I error (AR14298 (Roth), AR14645 (2d Roth)), and Vanda's studies demonstrated efficacy.

FDA, however, objects that Vanda did not prespecify a Type I error control specifically for the secondary patient-reported endpoints. AR18035-18036. FDA is wrong to contend this is grounds to disregard the evidence from these endpoints.

First, Vanda had no obligation to "prespecify" a special Type I error control method specific to the secondary subjective endpoints, and FDA points to none. *See* AR18035-18037. On the contrary, the *E9 Guidance* FDA references expressly provides that prespecifying a single primary endpoint controls for Type I error and that it is only when a sponsor uses "multiple *primary* variables" that FDA expects a Type I error explanation. FDA, *E9 Guidance*, *supra*, at 9, 33 (emphasis added). Vanda satisfied that obligation—by specifying a single primary endpoint for each trial. FDA cannot

disregard Vanda's secondary endpoints for failing to prespecify a Type I error control when FDA's own guidance confirms that an appropriate Type I error control is selecting a primary endpoint. *Id.* at 7. More, FDA previously approved Hetlioz® to treat Non-24 without a prespecified Type I error control for secondary endpoints, again confirming the absence of any such obligation. AR538-542, AR563.

Second, Vanda provided an expert declaration from a biostatistician, Dr. Platt, establishing that, given the overwhelmingly favorable results on Vanda's secondary endpoints, the likelihood that these results are "attributable to a false positive is *negligible*." AR14719 (emphasis added). And Dr. Roth explained that the favorable direction on all the secondary endpoints confirmed to him that there is a "low chance" these results all occurred due to chance. AR14300.

In other words, while FDA raises concern that there may be a Type I error, Vanda provided unrebutted evidence that there *is not* any Type I error that affects the ultimate efficacy conclusion.[12] FDA's ultimate conclusion—that there is not even a material dispute of fact as to Hetlioz®'s efficacy

[12] The order references a CDER reply—to which Vanda was not permitted to respond—that notes the same complaints about prespecification and raises certain limitations that are inherent to a meta-analysis. AR18037; AR18286-18290. Dr. Platt of course understands the limitations of a meta-analysis—he is an expert biostatistician after all. He consulted with Dr. Roth, a sleep-study expert, to design a statistically valid approach in the context of these studies. If FDA had any genuine basis for disagreement—

because Vanda did not prespecify a Type I error control for secondary endpoints (which it had no obligation to do (*supra* at 57-58))—cannot rationally follow given the evidence before the agency. *Cf. Weinberger*, 412 U.S. at n.17 ("[I]t may not be proper to deny a hearing on the ground that [a] study did not comply with [] regulation[s]" that "call for the exercise of discretion or subjective judgment in determining whether a study is adequate and well controlled."); *see also Edison*, 513 F.2d at 1071-1072 (setting aside final order denying NDA for lack of "adequate and well-controlled" studies and requiring agency to hold an evidentiary hearing on dispute whether proposed double-blind tests "are too dangerous to perform").

FDA's position that it can disregard all the secondary-endpoints evidence—which all supports the efficacy finding from the primary endpoints—because of a failure to prespecify a testing order is thus arbitrary and capricious.

C. FDA admits that its "additional concerns" cannot preclude approval.

Finally, although FDA noted in passing "additional concerns," it expressly did not find these an independent basis for its action. AR18039-18042. For good reason—because Vanda, with expert evidence, thoroughly explained why FDA's objections about eastward travel (AR14604-14605),

---

and it provided no evidence to that effect—a hearing is the appropriate mechanism to resolve such issues.

baseline polysomnograms (AR14598-14600), and dosing nights (AR14600-14601) were unfounded. *See* AR206-212 (collecting Vanda's evidence). FDA has thus admitted that these limitations cannot preclude approval assuming the Court agrees with our earlier arguments—and it should.

III. FDA'S ORDER VIOLATES THE APPOINTMENTS CLAUSE.

The Appointments Clause establishes a tripartite system for classifying official authority. First, "principal officers" are appointed by the President and confirmed by the Senate. *Edmond v. United States*, 520 U.S. 651, 659 (1997). Second, "inferior officers" may be appointed by the President with Senate confirmation, but Congress may also allow, by statute, selection by the President alone, by a court, or by a "Head[] of Department[]." *Lucia v. SEC*, 138 S. Ct. 2044, 2051 n.3 (2018). Finally, individuals who are neither principal nor inferior officers are mere "employees." *Id.* at 2051.

Because the "nature" of Dr. Bumpus's responsibilities was not "consistent" with her "method of appointment" (*United States v. Arthrex, Inc.*, 594 U.S. 1, 13 (2021)), FDA's action must be set aside.

A. Dr. Bumpus was not a principal officer.

Approving or denying a supplemental new drug application is an action that must be taken by an officer: The action imposes legal consequences, affects the rights of a drug applicant (*see* 21 U.S.C. §§ 331, 333, 355), binds the executive branch, and, ultimately, entails the exercise of

"'significant authority' in adjudicating the public rights of private parties." *Arthrex*, 594 U.S. at 23.

Because Dr. Bumpus issued a final decision, without any need for review by a superior official, her authority was proper only if she was a *principal* officer, appointed through presidential nomination and Senate confirmation. *Arthrex*, 594 U.S. at 6-16. But Dr. Bumpus was not so appointed. The only position within FDA subject to presidential appointment with advice and consent is the Commissioner of Food and Drugs. U.S. House of Reps., Committee on Oversight Reform, *Policy and Supporting Positions* 69 (Dec. 2020), perma.cc/D4BH-6PCR.

Because no FDA protocol or procedure authorizes routine review of her decisions by a principal officer, her action is unlawful. *Arthrex*, 594 U.S. at 23; *id*. at 41 (Breyer, J., concurring).

B. Dr. Bumpus was not a properly appointed inferior officer.

As the Supreme Court long ago explained, "[t]he head of a department has no constitutional prerogative of appointment to offices independently of the legislation of congress." *United States v. Perkins*, 116 U.S. 483, 485 (1886). That is, the Appointments Clause is not satisfied unless Congress has vested "the authority to appoint the inferior officer in a 'Head of Department.'" *United States v. Concord Mgmt. & Consulting LLC*, 317 F. Supp. 3d 598, 618 (D.D.C. 2018).

Congress never authorized Dr. Bumpus's appointment. No statute vests appointment authority for the Principal Deputy Commissioner in the head of the Department of Health and Human Services. This stands in stark contrast to other components of that Department. For the Social Security Administration, the Secretary is empowered to "appoint and fix the compensation of such officers and employees … as may be necessary for carrying out the functions of the Secretary under [chapter 7 of Title 42]." 42 U.S.C. § 913 (emphasis added).[13] No such authority exists with respect to FDA.[14] Dr. Bumpus thus does not occupy a position whose appointment Congress has directly "vest[ed] … in the President alone, in the Courts of Law, or in the Heads of Departments." U.S. Const. art. II, § 2, cl. 2.

CONCLUSION

The Court should reverse or alternatively vacate and remand FDA's order.

---

[13] *See also, e.g.*, 7 U.S.C. § 610(a) (similar); 20 U.S.C. § 3461(a) (similar); 49 U.S.C. § 323(a) (similar).

[14] 21 U.S.C. § 379d-3a allows the Secretary to "appoint outstanding and qualified candidates to scientific, technical, or professional positions … to support the" agency. *Id.* In authorizing "support" personnel to be hired into the "competitive service," Congress did not implicitly authorize a free-floating authority to appoint "officers."

Dated: June 24, 2024

Respectfully submitted,

/s/ *Paul W. Hughes*
PAUL W. HUGHES
SARAH P. HOGARTH
CHARLES SEIDELL
NICOLE WITTSTEIN
McDermott Will & Emery LLP
500 North Capitol Street NW
Washington, DC 20001
(202) 756-8000

Counsel for Petitioner
Vanda Pharmaceuticals Inc.

CERTIFICATE OF COMPLIANCE

Pursuant to Federal Rule of Appellate Procedure 32(g), I hereby certify that this brief:

(i) complies with the type-volume limitation of Rule 32(a)(7) because it contains 12,998 words, excluding the parts of the brief exempted by Rule 32(f) and Circuit Rule 32(e)(1); and

(ii) complies with the typeface requirements of Rule 32(a)(5) and the type style requirements of Rule 32(a)(6) because it has been prepared using Microsoft Office Word 2016 and is set in New Century Schoolbook LT Std font in a size equivalent to 14 points or larger.

Dated: June 24, 2024 /s/ *Paul W. Hughes*

CERTIFICATE OF SERVICE

I hereby certify that on June 24, 2024, I electronically filed the foregoing brief with the Clerk of this Court using the CM/ECF system, and counsel for all parties will be served by the CM/ECF system.

Dated: June 24, 2024 /s/ *Paul W. Hughes*

ADDENDUM

Addendum
Table of Contents

21 U.S.C. § 355(a) provides:

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug.

21 U.S.C. § 355(b)(1)(A) provides:

(b) Filing application; contents

(1)

(A) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as part of the application—

(i) full reports of investigations which have been made to show whether such drug is safe for use and whether such drug is effective in use;

(ii) a full list of the articles used as components of such drug;

(iii) a full statement of the composition of such drug;

(iv) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;

(v) such samples of such drug and of the articles used as components thereof as the Secretary may require;

(vi) specimens of the labeling proposed to be used for such drug;

(vii) any assessments required under section 355c of this title; and

(viii) the patent number and expiration date of each patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug, and that—

(I) claims the drug for which the applicant submitted the application and is a drug substance (active ingredient) patent or a drug product (formulation or composition) patent; or

(II) claims a method of using such drug for which approval is sought or has been granted in the application.

21 U.S.C. § 355(c)(1) provides:

(c) Period for approval of application; period for, notice, and expedition of hearing; period for issuance of order

(1) Within one hundred and eighty days after the filing of an application under subsection (b), or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(A) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) applies, or

(B) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

21 U.S.C. § 355(d) provides:

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that

(1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof;

(2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions;

(3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity;

(4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or

(5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or

(6) the application failed to contain the patent information prescribed by subsection (b); or

(7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular;

he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence. The Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decisionmaking, and the communication of the benefits and risks of new drugs. Nothing in the preceding sentence shall alter the criteria for evaluating an application for marketing approval of a drug.

21 U.S.C. § 355(e) provides:

(e) Withdrawal of approval; grounds; immediate suspension upon finding imminent hazard to public health

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds

(1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved;

(2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or

(3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or

(4) the patent information prescribed by subsection (c) was not filed within thirty days after the receipt of written notice from the Secretary specifying the failure to file such information; or

(5) that the application contains any untrue statement of a material fact:

Provided, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application submitted under subsection (b) or (j) with respect to any drug under this section if the Secretary finds

(1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (k) or to comply with the notice requirements of section 360(k)(2) of this title, or

the applicant has refused to permit access to, or copying or verification of, such rec-ords as required by paragraph (2) of such subsection; or

(2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or

(3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of.

Any order under this subsection shall state the findings upon which it is based. The Secretary may withdraw the approval of an application submitted under this section, or suspend the approval of such an application, as provided under this subsection, without first ordering the applicant to submit an assessment of the approved risk evaluation and mitigation strategy for the drug under section 355–1(g)(2)(D) of this title.

21 U.S.C. § 355(h) provides:

(h) Appeal from order

An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secre-

tary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of title 28. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28. The commencement of proceedings under this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

21 C.F.R. § 12.24(b) provides:

(b) A request for a hearing will be granted if the material submitted shows the following:

(1) There is a genuine and substantial issue of fact for resolution at a hearing. A hearing will not be granted on issues of policy or law.

(2) The factual issue can be resolved by available and specifically identified reliable evidence. A hearing will not be granted on the

basis of mere allegations or denials or general descriptions of positions and contentions.

(3) The data and information submitted, if established at a hearing, would be adequate to justify resolution of the factual issue in the way sought by the person. A hearing will be denied if the Commissioner concludes that the data and information submitted are insufficient to justify the factual determination urged, even if accurate.

(4) Resolution of the factual issue in the way sought by the person is adequate to justify the action requested. A hearing will not be granted on factual issues that are not determinative with respect to the action requested, e.g., if the Commissioner concludes that the action would be the same even if the factual issue were resolved in the way sought, or if a request is made that a final regulation include a provision not reasonably encompassed by the proposal. A hearing will be granted upon proper objection and request when a food standard or other regulation is shown to have the effect of excluding or otherwise affecting a product or ingredient.

(5) The action requested is not inconsistent with any provision in the act or any regulation in this chapter particularizing statutory standards. The proper procedure in those circumstances is for the person requesting the hearing to petition for an amendment or waiver of the regulation involved.

(6) The requirements in other applicable regulations, e.g., §§ 10.20, 12.21, 12.22, 314.200, 514.200, and 601.7(a), and in the notice promulgating the final regulation or the notice of opportunity for hearing are met.

21 C.F.R. § 314.200(g) provides:

(g) Summary judgment. A person who requests a hearing may not rely upon allegations or denials but is required to set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing with respect to a particular drug product specified in the request for hearing.

(1) Where a specific notice of opportunity for hearing (as defined in paragraph (a)(1) of this section) is used, the Commissioner will enter summary judgment against a person who requests a hearing, making findings and conclusions, denying a hearing, if it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or abbreviated application or the withdrawal of approval of the application or abbreviated application; for example, no adequate and well-controlled clinical investigations meeting each of the precise elements of § 314.126 and, for a combination drug product, § 300.50 of this chapter, showing effectiveness have been identified. Any order entering summary judgment is required to set forth the Commissioner's findings and conclusions in detail and is required to specify why each study submitted fails to meet the requirements of the statute and regulations or why the request for hearing does not raise a genuine and substantial issue of fact.

(2) When following a general notice of opportunity for a hearing (as defined in paragraph (a)(1) of this section) the Director of the Center for Drug Evaluation and Research concludes that summary judgment against a person requesting a hearing should be considered, the Director will serve upon the person requesting a hearing by registered mail a proposed order denying a hearing. This person has 60 days after receipt of the proposed order to respond with sufficient data, information, and analyses to demonstrate that there is a genuine and substantial issue of fact which justifies a hearing.

(3) When following a general or specific notice of opportunity for a hearing a person requesting a hearing submits data or information of a type required by the statute and regulations, and the Director of the Center for Drug Evaluation and Research concludes that summary judgment against the person should be considered, the Director will serve upon the person by registered mail a proposed order denying a hearing. The person has 60 days after receipt of the proposed order to respond with sufficient data, information, and analyses to demonstrate that

there is a genuine and substantial issue of fact which justifies a hearing.

(4) If review of the data, information, and analyses submitted show that the grounds cited in the notice are not valid, for example, that substantial evidence of effectiveness exists, the Commissioner will enter summary judgment for the person requesting the hearing, and rescind the notice of opportunity for hearing.

(5) If the Commissioner grants a hearing, it will begin within 90 days after the expiration of the time for requesting the hearing unless the parties otherwise agree in the case of denial of approval, and as soon as practicable in the case of withdrawal of approval.

(6) The Commissioner will grant a hearing if there exists a genuine and substantial issue of fact or if the Commissioner concludes that a hearing would otherwise be in the public interest.

(7) If the manufacturer or distributor of an identical, related, or similar drug product requests and is granted a hearing, the hearing may consider whether the product is in fact identical, related, or similar to the drug product named in the notice of opportunity for a hearing.

(8) A request for a hearing, and any subsequent grant or denial of a hearing, applies only to the drug products named in such documents.